REMARKS

Claims 13-20 have been amended to recite a:

> "method for the treatment or prophylaxis of a pathology affecting the internal tissues of an eye, excluding the pathologies affecting the optic nerve, comprising the administration of a composition comprising from 10 to 500 μg/ml of nerve growth factor over ~~onto~~ the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues."

Support for these amendments is found in the specification at, for example, page 1, lines 4-12, page 8, line 12 to page 9, line 5, page 9, line 30 to page 9a, line 18, and in original claim 9. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Claims 21-24 have been amended to recite a:

> "method for the treatment or prophylaxis of a pathology affecting the internal tissues of an ~~the~~ eye, excluding retinal pathologies and pathologies affecting the optic nerve, comprising the administration of a composition comprising nerve growth factor over the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues."

Support for these amendments is found in the specification at, for example, page 1, lines 4-12, page 8, line 12 to page 9, line 5, page 9, line 30 to page 9a, line 18.

New claims 25-36 recite a:

> "method for the treatment or prophylaxis of a pathology affecting the internal tissues of an eye, comprising the administration of a composition comprising from 200 to 500 μg/ml of nerve growth factor over the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues."

Support for these amendments is found in the specification at, for example, page 1, lines 4-12, page 9, line 30 to page 9a, line 18, page 12, lines 8-21, and in original claims 1-12. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

Anticipation Rejection

Claims 13-20 were rejected under 35 USC § 102(a) as being anticipated by WO 98/10785 ("Okamoto"). (Paper No. 9 at 2.)

Okamoto[1] discloses "remedies for optic nerve function disorders ... and contact lenses containing these remedies."

In making the rejection, the Examiner asserted that "[the] patent provides an ophthalmic composition for subconjunctival and ocular injection to treat optic nerve disorders, said composition comprising NGF in an amount of 10^{-3} to 2 x 10^{5} μg/l (See pp. 3-4) ...." (Paper No. 9 at 2.)

The Examiner then concluded that "[t]he method disclosed by the patent meets the limitations of claims 13-20 ... as it contemplates methods comprising administering a composition comprising nerve growth factor (NGF) to a subject in need thereof for the treatment of a pathology affecting the internal tissue of an eye." (Paper No. 9 at 2.)

The Examiner further stated that "[Okomoto] discloses [a] composition comprising NGF in an amount of 10^{-3} to 2 x 10^{5} μg/l ... corresponding to a maximum amount of 200 μg/ml, *which is in the range claimed by Applicant in claim 1 [sic claim 13] and corresponds*

[1] The Applicant asked the Examiner in the Response filed March 27, 2003 (see p. 7, n. 2) to please provide an English translation of Okamoto, if one was available, but no translation was provided with the Examiner's Final Action.

to the amount claimed by Applicant in claims 19 and 24. Thus the reference anticipates the claimed invention." (Paper No. 9 at 5.) (emphasis added).

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). In a §102 rejection there must be no difference between what is claimed and what is disclosed in the applied reference. *In re Kalm*, 154 USPQ 10, 12 (CCPA 1967); *Scripps v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

Initially, we note that claims 13-20 have been amended to exclude the treatment of pathologies of the optic nerve. Thus, in view of the amendments and remarks set forth above, withdrawal of the §102(a) rejection of claims 13-20 is respectfully requested.

New claim 25 recites a "method for the treatment or prophylaxis of a pathology affecting the internal tissues of an eye, comprising the administration of a composition comprising from 200 to 500 μg/ml of nerve growth factor over the ocular surface of a subject in need thereof, wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues."

The disclosed range in Okomoto of 10^{-3} to 2 x 10^{5} **μg/l** (i.e. .000001 to 200 **μg/ml**) is ***much broader*** than the claimed range of 200 to 500 **μg/ml and does not overlap with that range**. Furthermore, Okamoto does not disclose a specific amount or value within the claimed range.

The MPEP § 2131.03 makes clear that for a range to be anticipated by the prior art, the prior art must disclose a range within, overlapping, or touching the claimed range so that

the prior art range discloses the claimed range with "sufficient specificity." (See MPEP § 2131.03 at 2100-72). The MPEP § 2131.03 further states:

> "When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. The unexpected results may also render the claims unobvious. The question of "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching. See MPEP § 2131.02 . A 35 U.S.C. 102/103 combination rejection is permitted if it is unclear if the reference teaches the range with "sufficient specificity." The examiner must, in this case, provide reasons for anticipation as well as a motivational statement regarding obviousness. Ex parte Lee 31 USPQ2d 1105 (Bd. Pat. App. & Inter. 1993) (expanded Board). For a discussion of the obviousness of ranges see MPEP § 2144.05 (*Id.*)"

The range disclosed by Okomoto, namely 10^{-3} to 2 x 10^{5} **µg/l** is a range which touches the claimed range. However, no specific examples falling within the claimed range are disclosed. The only actual data available, given in the examples, recite NGF concentrations, in an ophthalmic solution, of **0.04 and 0.02 µg/ml**. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." As explained above, what constitutes "sufficient specificity" is fact dependent. Here, the Examiner has not provided any reasoning why the disclosed range of

10^{-3} to 2 x 10^{5} **µg/l (equivalent to 0.000001 to 200 µg/ml)** would anticipate a claimed range of 200 to 500 **µg/ml.**

The Examiner's concludes in the Final Rejection that:

> "[Okomoto] discloses [a] composition comprising NGF in an amount of 10^{-3} to 2 x 10^{5} µg/l ... corresponding to a maximum amount of 200 µg/ml, which is in the range claimed by Applicant in claim 1 [sic claim 13] and corresponds to the amount claimed by Applicant in claims 19 and 24. Thus the reference anticipates the claimed invention"

This form of analysis is inconsistent with the case law and the MPEP. The fact that the maximum value range of 200 µg/ml touches applicant's claimed range does not end the analysis. (Paper No. 9 at 5.) (emphasis added).

The question of "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching. See MPEP § 2131.03. The range disclosed in Okomoto is from .000001 to 200 µg/ml, which is an extemely broad range of concentrations *compared with* the claimed 200-500 µg/ml. See MPEP § 2131.02 (discussing the "clearly envisage" standard) and *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962) (limited genus of 20 compounds sufficient to anticipate). Here, there are at least 200 million[2] possibilities for the amount of NGF in Okomoto (which is 10 million times the size of the genus disclosed in *Petering*).

Moreover, the Examiner's reasoning that because "**200 µg/ml...<u>is in the range</u> claimed by Applicant in claim 1 .... Thus the reference anticipates the claimed invention"** has been specifically rejected by the Board. Recently, the Board in *Ex parte Itoh*, 2000 WL

[2] 200 µg/ml divided by .000001µg/ml (as a concentration value) is 200 million.

33914618, *6 (BPAI 2000) (unpublished) reversed an examiner for making a similar rejection.

There, the Board explained:

> "We will not sustain the rejection of claims 2 to 6 under 35 U.S.C. § 102.
>
> "Dependent claim 2 adds to parent claim 1 the further limitation that "said main grooves are formed by being inclined at an angle in a range from 7° to 25° with respect to a pipe axis." Dependent claims 3 to 6 add to parent claim 1 the further limitation that "said auxiliary grooves are formed at a spiral angle in a range of +-5° with respect to a pipe axis."
>
> "The appellants argue (brief, pp. 6-8) that the above noted limitations are not met by Chiang. We agree. It is an elementary principle of patent law that when something is claimed as having a maximum value ranging to a minimum value, the claim is "anticipated" if the prior art shows any one value within the claimed range. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985).
>
> "**When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation.** In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. See Ex parte Lee, 31 USPQ2d 1105, 1106-07 (Bd. Pat. App. & Int. 1993).
>
> "**In this case, Chiang does not disclose *any one value* falling within the range set forth in either claim 2 or claim 3. Moreover, it is our view that a value falling within the range set forth in claim 2 or claim 3 is not set forth in Chiang with "sufficient specificity" to constitute an anticipation.**" For the reasons set forth above, the decision of the examiner to reject claims 2 to 6 under 35 U.S.C. § 102 is reversed."

Id. at *6 (emphasis added). See also *Ex parte Matsumoto*, 1999 WL 33244576, *4 (BPAI 1999) (unpublished) ("However, while the water absorption range overlaps with appellant's range of less than 5 wt%, we do not consider that the water absorption of less than 10% disclosed by Lambert to be a description of sufficient specificity to constitute a description within the purview of 35 U.S.C. § 102(b) anticipation. Lambert does not specifically disclose a range of less than 5 wt% nor does Lambert give an example having a value of less than 5 wt%. For this reason alone, we cannot sustain the examiner's rejection of claims 12, 13, 16-22 and 25-30 under 35 U.S.C. § 102(b) as anticipated by Lambert.") (citations omitted); *Ex parte Gaffar*, 1995 WL 1774381 (BPAI 1995) (unpublished) (reversing an examiner's §102 rejection because the reference does not disclose the claimed subject matter with "sufficient specificity" to constitute an anticipation) and *Ex parte Macedo*, 2002 WL 130560 (BPAI 2002) (unpublished) (same).

Here, Okomoto does not disclose any one value falling within the range set forth in the claims. Okomoto only discloses a range which touches, but does not overlap the claimed range, but no specific examples falling within the claimed range are disclosed. (In fact, the specific examples are nowhere near the presently claimed range). In addition, Okomoto does not disclose the claimed range with "sufficient specificity" to constitute an anticipation. Therefore, it is respectfully submitted that the rejection be withdrawn.

Finally, in order for Okomoto to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368,

1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). As noted in an earlier paper, experiments were run, using the methods described in his specification, which showed that concentrations of NGF employed by Okamoto in his examples (0.02 and 0.04 μg/ml) are at least 25 times lower than the lowest concentrations needed to show any trace of NGF passing through the cornea and taken into the internal occular tissues. This data can be formally presented to the Examiner, if she would deem it helpful.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejection, and allowance of the claims are respectfully requested.

Obviousness Rejection

Claims 13-24 were rejected under 35 USC §103 as being obvious over Finkenaur *et al.*, EPA 0312208A1 ("Finkenaur"). (Paper No. 9 at 3.)

Finkenaur discloses "[g]el formulations containing polypeptide growth factors having human mitogenic or angiogenic activity are provided. The gel formulations are useful for topical or incisional ***wound*** healing for cutaneous wounds, in the anterior chamber of the eye and other ophthalmic wound healing." (Abstract.)

In making the rejection, the Examiner asserted that "Finkenaur ... discloses the use of a composition comprising a polypeptide growth factor, in particular NGF, in a

concentration of 1-500 μg/ml for the treatment of wounds ... [and] teaches that the gels of the invention can be in the form of eye drop formulations or solutions and includes surgically induced ophthalmic wounds, in particular subconjunctival wounds, among the wounds healed by the composition of the invention ...." (Paper No. 9 at 3.)

The Examiner acknowledged, however, that "Finkenaur et al. does not specifically mention that the compositions of the invention are administered into the ocular surface ...." (*Id.*)

The Examiner then contended that "[i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Finkenaur et al. to device methods for the treatment of pathologies affecting the internal tissue of the eye, comprising administering NGF in the amount disclosed in the publication. The expected result would have been successful methods of treatment of the pathology in the eye." (*Id.* at 4.)

The Examiner then concluded that "[b]ecause of the teachings of Finkenaur et al., that NGF is effective in treating ophthalmic wounds, including internal wounds, one of ordinary skill in the art would have a reasonable expectation of success that the methods claimed in the instant application would be successful. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made." (*Id.*)

The Examiner also stated that:

> "Applicant's argument, that Finkenaur et al. does not teach or suggest that NGF is able to pass through the ocular tissues, so that the composition is applied only to the ocular surface, it is noted that the reference teaches that the compositions of the invention may be in the form of eye drop formulations and ophthalmic irrigating solutions, which are suited for application into the ocular surface of the eye, as claimed by Applicant. ***Furthermore, the***

> ***features upon which Applicant relies (i.e., passing through the ocular tissues) are not recited in the rejected claims.***" (Id. at 5-6 (emphasis added)).

Claims 13-24 have been amended to recite administering "over the ocular surface ... wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues." New claims 25-36 also contain the same limitations.

We note that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

Moreover, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). See also MPEP § 2143.03.

Finkenaur is discussed at p. 5 of applicant's specification. The specification states:

> With specific reference to the disorders affecting ***the exposed ocular surface***, i.e. corneal and conjunctival diseases, EP-A-0312208 discloses gel formulations for use in the treatment of epithelial lesions and epithelial pathologies in general, including lesions and pathologies of the ocular surface. The said formulations contain an active ingredient which may be indiscriminately chosen among the various molecules whose name contains the expression "growth factor". Although ***the description is exclusively concerned with the epidermal growth factor (EGF)***

> as the preferred active ingredient, and although activity data (*in vitro*) and formulation examples are given only for EGF, other growth factors are mentioned as well, such as FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), TGF-α (transforming growth factor) or the NGF itself. The said growth factors are apparently presented as a family of molecules having equivalent characteristics and biological activity as EGF. As a matter of fact, at the current state of the knowledge, ***it is undisputed that the said growth factors have different specific targets and that they often have conflicting effects, so that they are not considered as biologically equivalent to each other.*** (emphasis added).

The various growth factors mentioned above are different individual molecules, with a different amino acid sequence, structure and molecular weight, and, above all, different receptor sites and different biological activity. For instance, EGF is a 53 amino acid polypeptide having a molecular weight of about 6000 dalton, while NGF is a 140 kdalton molecular complex. The applicant is especially and exclusively claiming a method based on NGF. Finkenaur only incidentally mentioned NGF and does NOT teach the method claimed.

Finkenaur teaches the use of EGF for the treatment of incisional wounds, based on the disclosed mitogenic properties of this compound. (See p. 2, lines 17-24). Finkenaur discloses the direct application of the product on a wound, whether it be a surface wound or an internal wound. (See p. 4, lines 7-13). The Examiner's conclusion that "[b]ecause of the teachings of Finkenaur et al., that NGF is effective in treating ophthalmic wounds, including internal wounds, one of ordinary skill in the art would have a reasonable expectation of success that the methods claimed in the instant application would be successful" is in error. (Paper No. 9 at 4.) The method as claimed is for treatment by administering "*over the ocular surface ... wherein said nerve growth factor passes through the external tissues of said eye to said internal*

tissues." The claimed invention is not administered to a wound, a cut or anything that interrupts the continuity of the ocular surface, since the product is not intended to be applied **directly on the site to be treated**, but is expected **to pass through the ocular tissues**, and to reach some internal tissues where its action is needed. Finkenaur, however, is concerned with direct application of the product on the wound. The rejection is void of any suggestion that Finkenaur discloses the unexpected claimed finding that NGF is able ***to pass through the ocular tissues***, so that the product need only be applied to the ocular surface, not directly to the affected area or wound. Thus the rejection is factually and legally deficient and should be withdrawn.

The Examiner states that Finkenaur "contemplates" the presently claimed method by administering NGF to treat a pathology affecting the internal tissue of an eye. (Paper No. 6 at 2.) The amended claims and newly added claims, however, recite that the treatment occurs by administering "over the ocular surface" and "wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues." Thus, the rejection does not – and cannot – identify where in Finkenaur it is disclosed that the nerve growth factor passes through the external tissues of the eye to the internal tissues. Thus the rejection is factually and legally deficient and should be withdrawn.

CONCLUSION

In view of the foregoing, favorable action on the merits, including entry of the amendments, withdrawal of the rejections, and allowance of all the claims, are respectfully requested. If the Examiner has any questions regarding this paper, please contact one of the undersigned attorneys.

Respectfully submitted,

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